The effect of body composition on prognosis in critically ill COVID-19 patients

Sarcopenia in ICU patients diagnosed with COVID-19

Ismail Beypinar[1], Murat Bayav[2], Anil Ucan[3], Serdar Efe[4]
[1]Department of Medical Oncology, Eskişehir City Hospital
[2]Department of Radiology, Eskişehir City Hospital
[3]Department of Internal Medicine, Eskişehir City Hospital
[4]Department of Intensive Care, Eskişehir City Hospital, Eskişehir, Turkey

Abstract

Aim: Although limited risk factors were observed with the accumulated evidence during the SARS-CoV-2 (COVID-19) pandemic, there is still a lack of evidence for markers distinguishing asymptomatic-mild disease from severe disease. In this study, we aimed to evaluate the prognostic impact of sarcopenia and visceral adipose tissue in ICU patients treated for COVID-19.
Material and Methods: The study designed as a retrospective cross-sectional study for evaluating the effect of prognostic radiologic features in COVID-19 infected patients. The patient characteristics, intubation status and dates, transfer to ICU, and last control or death dates were recorded. Axial CT images, including all abdominal muscles, total skeletal muscle area, were calculated. The total and psoas sarcopenia index (PSI) was calculated by dividing the square of the patient's height by the square meter (cm2/m2). Also, axial CT images of the body fat subcutaneous adipose and visceral adipose tissue distribution areas were calculated in cm2 using threshold values of -30 to -190 for adipose tissue.
Results: In the study population, there were nine deaths that occurred among male patients. In univariate analysis, chronic obstructive pulmonary disease and PSI were found to be related to prognosis. The median survival was 14 days in PSI low group. The prognostic effect of the PSI was still valid in the male population. Other factors had no relationship with survival in univariate analysis. In multivariate analysis, the prognostic effect of TSI and PSI was related to prognosis, while COPD lost its prognostic effect.
Discussion: In this study, we found a new prognostic factor in critically ill COVID-19 patients, which may be a new area of interest. In contrast to other studies, we found no effect of BMI and visceral adipose tissue on mortality in COVID-19 patients treated in ICU. This feasible method needs further evaluation and validation with prospective studies in a large patient population.

Keywords

COVID-19; Mortality; Sarcopenia; Visceral adipose tissue; Prognosis; Critically ill patients

Introduction

SARS-CoV-2 (COVID-19) is a single-stranded RNA spherical virus which has glycoprotein spikes [1]. Multiple subtypes of coronaviruses have the capability of infecting humans. The major subgroups which have severe infection capacity are COVID-19, MERS, and SARS-CoV-1 [2]. The primary target of the COVID-19 is angiotensin-converting enzyme-2 (ACE-2) located on the alveolus and ciliated bronchial epithelium. Airborne droplets were shown to be the direct dissemination way of the viral particles [3]. Cough, fever, and shortness of breath are the most frequent symptoms of the disease. It has been reported that myocardial damage, respiratory and renal failure are the leading reasons for death in COVID-19 patients [4]. Approximately 200.000 deaths, confirmed by the World Health Organization, occurred related to COVID-19 till April 25, 2020 worldwide [5].

According to the literature, the groups most affected by COVID-19 were immunocompromised and older adults. High rates of respiratory failure during the disease are the major problem in COVID-19 infection [6]. Although limited risk factors with the accumulated evidence were observed during the pandemic, there is still a lack of evidence for markers distinguishing asymptomatic-mild disease from severe disease [7].

Catabolism of the main skeletal muscle proteins is a frequent phenomenon for chronic conditions such as cancer and chronic obstructive lung disease [8]. Also, cachexia is known to be related to increased mortality in cancer patients [9]. Differences in body composition between males and females have been observed in previous studies in both healthy subjects, patients with cirrhosis, or cancer. Muscle tissue was enlarged in males, while females had enlarged adipose tissue [10]. Sarcopenia is one of the new areas of interest in cancer patients in relation to a clinical marker [11]. Obesity, according to body mass index (BMI), is associated with a decreased treatment response in breast cancer patients [12]. Obese patients are not uniform; some patients remain metabolically stable, which is called the 'obesity paradox' [13]. In addition, sarcopenia can be masked by increased BMI, which leads to the phenomenon of sarcopenic obesity [14]. For these reasons, BMI is not a reliable marker for estimating body composition and disease prognosis.

A new study reported that increased BMI might be related to increased mortality in patients hospitalized for COVID-19 [15]. Computed tomography (CT) is a reliable method to evaluate the muscle quality and adipose tissue [16].

To our knowledge, there are no studies investigating the prognostic effect of sarcopenia in critically ill patients hospitalized for COVID-19. In this study, we try to evaluate the prognostic impact of sarcopenia and visceral adipose tissue in ICU patients treated for COVID-19.

Material and Methods

Study Participants

The archive records of patients, who were diagnosed with COVID-19 between 11th March 2020 and 15th June 2020 at the Eskişehir City Hospital Intensive Care Unit, were retrospectively analyzed. Patients with COVID-19 were diagnosed using PCR. Oropharyngeal and nasal swabs were obtained in PCR samples. Patients who do not have PCR testing or have inadequate diagnosis were excluded. Patient characteristics, height, weight, comorbidities such as diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD), smoking status, diagnosis, intubation status and dates, transfer to ICU, and last control or death dates were recorded. The exclusion criteria were lack of adequate diagnosis, CT images, and follow-up.

Ethics

The study was approved by the Turkish Ministry of Health and the Ethics Committee of the Faculty of Medicine at Eskişehir Osmangazi University (approval number 2020/277) and was carried out in accordance with the Declaration of Helsinki principles and all applicable regulations.

Statistical analysis

Statistical analysis of the study was performed using SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL). Descriptive data were presented as either means or median for continuous variables, frequencies and percentages were reported for categorical variables. ROC analysis was performed to determine the optimal cut-off value, but if an optimal cut-off value cannot be determined, the median values will be used in the statistical analysis. Pearson's X^2 test was used to assess the associations in categorical variables. OS curves were estimated by the Kaplan-Meier product-limit method. Life tables were established to determine the proportional survival analysis.

Body composition assessment and CT analysis

The first CT images obtained in the emergency room or in the patient's clinic were used in the study to avoid calculating COVID-19 induced sarcopenia. On axial CT images, including all abdominal muscles (psoas, erector spinae, quadratus lumborum, external and internal oblique, and rectus abdominis), total skeletal muscle area (SMA) was calculated from the third lumbar vertebrate (Figure 1). The total and psoas sarcopenia index (TSI-PSI) was calculated by dividing the square of the patient's height by the square meter (cm^2/m^2). Also, axial CT images of the body fat subcutaneous adipose and visceral adipose tissue distribution (VAT, SAT) areas were calculated in cm^2 using threshold values of -30 to -190 for adipose tissue (Figure 2).

Results

Thirty-six patients were included in the study. Four patients were excluded due to a lack of adequate imaging procedures. The counts of male and female patients in the study were 28 and 8, respectively. The median age of the study population was 68 years. The median weight, height, and BMI of the study population were 80 kilograms, 1.7 meters, and 26,8 kg/m², respectively. The demographic features of the study population are described in Table 1.

In the study population, there were nine deaths that occurred among male patients. No death was observed in female patients. In univariate analysis, COPD and PSI were found to be related to prognosis (p=0,001, p=0,010). Although median survival was not reached in the high PSI group, PSI had a relationship with prognosis (Figure 3). The median survival was 14 days in the low PSI group. The prognostic effect of the PSI

was still valid in the male population. (p=0,007) Gender, DM, HT, CAD, TSI, VAT, BMI (categorized for both 25 and 30 kg/m²) had no relationship with survival in univariate analysis (Table 2). In multivariate analysis, the prognostic effect of TSI and PSI was related to prognosis, while COPD lost its prognostic effect (p=0,044; p=0,035; p=0,33).

Table 1. The comparative features of the study population according by gender

Features	n (%)	n (%)	p-value
Gender	Male	Female	
	28 (77)	8 (23)	N/A
Age (years)	72	66	0,16
Weight (kg)	80	80	0,74
Height (m)	1,75	1,60	0,008
BMI (kg/m²)	25,6	30,3	0,22
DM	11/28 (39,3)	4/8 (50)	0,58
HT	7/28 (25)	4/8 (50)	0,17
Coronary Artery Disease	5/28 (17,9)	2/8 (25)	0,65
COPD	8/28 (28,6)	0/8 (0)	0,08
Rheumatic Disease	1/28 (3,6)	1/8 (12,5)	0,06
Chronic Corticosteroid Utility	1/27 (3,7)	1/8 (12,5)	0,34
Typical CT images	27/28 (96,4)	7/8 (87,5)	0,33
Total adipose tissue (mm²)	432,3	504,5	0,22
Visceral adipose tissue (mm²)	244,3	216,5	0,68
Subcutaneous adipose tissue (mm²)	173,6	274,7	0,22
Total muscle area (mm²)	144,5	99,2	0,045
Psoas muscle area (mm²)	13,7	7,5	0,006
Total Sarcopenia index	45,9	38,1	0,22
Total Psoas index	4,1	2,7	0,26

BMI: Body Mass Index, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CT: Computed Tomography

Figure 1. Area measurements of the paraspinal, psoas, and abdominal wall muscle groups at the third lumbar vertebra level (green areas)
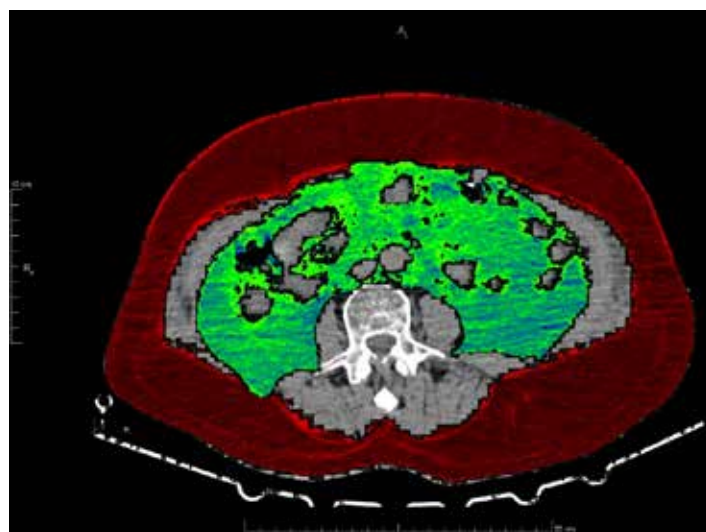

Figure 2. Combined image of visceral adipose tissue (green-blue) and subcutaneous adipose tissue (red) in the range of -190 to -30 HU at the level of third lumbar vertebra
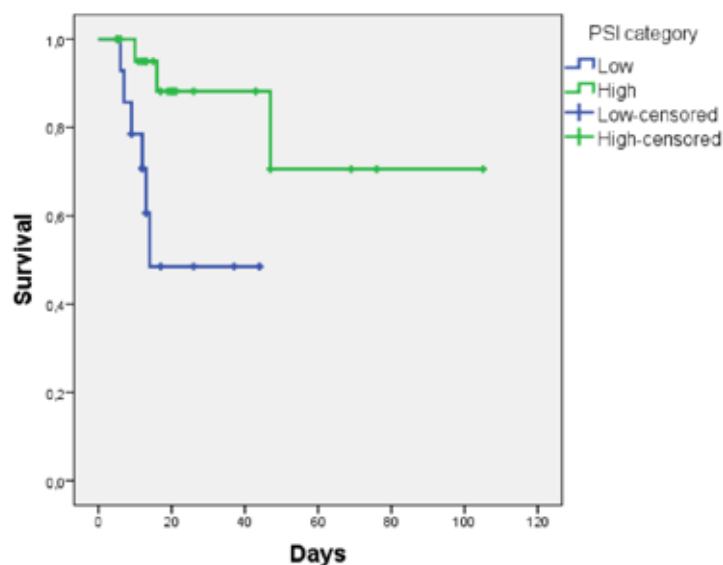
Table 2. Univariate analysis of the features of the study population

Features			p-value
Gender	Male	Female	
Median OS (days)	NR	NR	0,13
DM	Yes	No	
Median OS (days)	47	NR	0,45
HT	Yes	No	
Median OS (days)	NR	47	0,74
CAD	Yes	No	
Median OS (days)	NR	NR	0,67
COPD	Yes	No	
Median OS (days)	12	NR	0,001
PSI	Low	High	
Median OS (days)	14	NR	0,010
TSI	Low	High	
Median OS (days)	NR	NR	0,18
VAT	Low	High	
Median OS (days)	NR	NR	0,4
BMI (cut-off 25)	Low	High	
Median OS (days)	NR	NR	0,46

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, PSI: Psoas Sarcopenia Index, TSI: Total Sarcopenia Index, VAT: Visceral Adipose Tissue, BMI: Body Mass Index, NR: Not Reached

Figure 3. Patient survival chart by PSI category

Discussion

To our knowledge, this is the first study that evaluates the prognostic effect of sarcopenia in ICU patients. In our research, TSI and PSI were found to be an independent risk factor in COVID-19 infected ICU patients.

COVID-19 is known to have high mortality in the geriatric population. Conditions such as sarcopenia and frailty are frequently seen in the elderly [17]. Sarcopenia is defined as the loss of a prominent muscle tissue that is related to increased vulnerability to stressors [18]. Previous studies have shown a relationship between sarcopenia and ICU mortality [19]. Interestingly, COVID-19 infection was found to induce weight loss in animal models via interferon-gamma and tumor necrosis factor-alpha. This effect disappeared after the treatment [20]. Regulations, including social isolation during the pandemic, were strictly applied, especially to the elder population, which may accelerate muscle loss in a short period. Also, chronic conditions such as DM and COPD are responsible for sarcopenia in this group [21]. Although some new reports have been published, which have shown a relationship between high BMI and poor outcome in COVID-19 infection, no literature is available investigating sarcopenia in this condition. The death rates were higher in countries with a high prevalence of obesity, such as the United States of America (USA), Canada, the United Kingdom, and Mexico. This phenomenon was speculated to be related to sarcopenia, DM, CAD, increased function of the renin-angiotensin-aldosterone system (RAAS), obstructive sleep apnea, and deficiency of vitamin D. In the USA, a single-center experience showed that obesity and male gender are independent risk factors for COVID-19 infection [15]. In addition, a study investigating patient outcomes in China reported more symptoms and a severe disease course with increasing BMI [23]. In contrast to this literature, we did not found a significant relationship between BMI and COVID-19 infection, which might be related with sarcopenic obesity phenomenon. This result was supported by increased BMI but low mortality in female patients in the study population. Also, increased visceral adipose tissue was speculated to be a reservoir to the virus, which might induce an abnormal cytokine release and cause a poor outcome [24]. In our study, we found no relationship between visceral adipose tissue and increased mortality in critically ill patients. Although obstructive sleep apnea might be related to increased mortality due to obesity, no data were available in our study [25].

The limitations of this study were the small sample size, and the retrospective nature of the study made it hard to evaluate the outcomes. Although the first images were used to assess sarcopenia on CT images, the early period of the disease might affect the body composition. No deaths were observed in female patients, which might inflict the strong prognostic effect of sarcopenia in this patient group.

Conclusion

In this study, we found a new prognostic factor in critically ill COVID-19 patients, which may be a new area of interest. In contrast to other studies, we found no effect of BMI and visceral adipose tissue on mortality in COVID-19 patients treated in ICU. This comfortable and applicable method needs further evaluation and validation with prospective studies in a large patient population.

References

1. Wassenaar TM, Zou Y. 2019_nCoV/SARS-CoV-2: rapid classification of betacoronaviruses and identification of Traditional Chinese Medicine as potential origin of zoonotic coronaviruses. Lett Appl Microbiol. 2020;70(5):342–8. DOI:10.1111/lam.13285.
2. Gorbalenya A, Baker S, Baric R, de Groot R, Drosten C, Gulyaeva A, et al. Severe acute respiratory syndrome-related coronavirus : The species and its viruses – a statement of the Coronavirus Study Group. Nat Microbiol. 2020; DOI:10.1101/2020.02.07.937862.
3. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J Med Virol 2020;92:455–9. DOI:10.1002/jmv.25688.
4. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med. 2020;35(5):1545–9. DOI:10.1007/s11606-020-05762-w.
5. Livingston E, Bucher K, Rekito A. Coronavirus Disease 2019 and Influenza 2019-2020. JAMA. 2020;323(12):1122. DOI:10.1001/jama.2020.2633.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395 (10223):507–13. DOI:10.1016/S0140-6736(20)30211-7.
7. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110–18. DOI:10.1016/j.jaci.2020.04.006.
8. van de Bool C, Gosker HR, van den Borst B, Op den Kamp CM, Slot IGM, Schols AMWJ. Muscle Quality is More Impaired in Sarcopenic Patients With Chronic Obstructive Pulmonary Disease. J Am Med Dir Assoc. 2016;17:415–20. DOI:10.1016/j.jamda.2015.12.094.
9. Johns N, Stephens NA, Fearon KCH. Muscle wasting in cancer. Int J Biochem Cell Biol 2013;45(10):2215–29. DOI:10.1016/j.biocel.2013.05.032.
10. Blaak E. Gender differences in fat metabolism. Curr Opin Clin Nutr Metab Care. 2001;4(6):499–502. DOI:10.1097/00075197-200111000-00006.
11. Ligibel JA, Wollins D. American society of clinical oncology obesity initiative: Rationale, progress, and future directions. J Clin Oncol. 2016;34(35):4256–60. DOI:10.1200/JCO.2016.67.4051.
12. Fontanella C, Lederer B, Gade S, Vanoppen M, Blohmer JU, Costa SD, et al. Impact of body mass index on neoadjuvant treatment outcome: a pooled analysis of eight prospective neoadjuvant breast cancer trials. Breast Cancer Res Treat. 2015;150(1):127–39. DOI:10.1007/s10549-015-3287-5.
13. Denis GV, Obin MS. "Metabolically healthy obesity": Origins and implications. Mol Aspects Med. 2013;34(1):59–70. DOI:10.1016/j.mam.2012.10.004.
14. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629–35. DOI:10.1016/S1470-2045(08)70153-0.
15. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity is associated with higher in-hospital mortality in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108. DOI:10.1016/j.metabol.2020.154262.
16. Shen W, Punyanitya M, Wang ZM, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333–8. DOI:10.1152/japplphysiol.00744.2004.
17. Koff WC, Williams MA. Covid-19 and Immunity in Aging Populations — A New Research Agenda. N Engl J Med. 2020; 383(9):804-5. DOI:10.1056/nejmp2006761.
18. Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: Two sides of the same coin. Front Aging Neurosci. 2014; 6:192. DOI:10.3389/fnagi.2014.00192.
19. Toptas M, Yalcin M, Akkoc E, Demir E, Metin C, Savas Y, et al. The relation between sarcopenia and mortality in patients at intensive care unit. Biomed Res Int. 2018; 2018:5263208. DOI:10.1155/2018/5263208.
20. Chan JFW, Zhang AJ, Yuan S, Poon VKM, Chan CCS, Lee ACY, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019

(COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis. 2020; DOI:10.1093/cid/ciaa325.

21. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. J Nutr Heal Aging. 2018; DOI:10.1007/s12603-018-1139-9.

22. Zores F, Rebeaud ME. COVID and the Renin-Angiotensin System: Are Hypertension or Its Treatments Deleterious? Front Cardiovasc Med. 2020; DOI:10.3389/fcvm.2020.00071.

23. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. Diabetes Care. 2020; DOI:10.2337/dc20-0576.

24. Ryan PMD, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019? Obesity. 2020; DOI:10.1002/oby.22843.

25. Pazarlı AC, Ekiz T, İlik F. Coronavirus disease 2019 and obstructive sleep apnea syndrome. Sleep Breath. 2020; DOI:10.1007/s11325-020-02087-0.